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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/681,788
Filing Date: October 08, 2003
Appellant(s): ZAGHOUANI ET AL.

David B. Fournier
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 1/30/12 appealing from the Office action mailed 7/29/11.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

An Appeal Brief was filed in continuation-in-part application U.S. 11/290,070 on 7/11/11; a Reply Brief was filed on 12/19/11. An Appeal Brief was filed in continuation-in-part application U.S. 11/425,084 on 7/11/11; a Reply Brief was filed on 12/19/11.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 1-5, 7, 13, 15-19, 22-24, and 26-30.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner.

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

Autoimmune shares collapse on Colloral data in rheumatoid arthritis. *Marketletter*. Marketletter Pubs (UK) 1999.

DONG, V.M., et al. Transplantation tolerance: The concept and its applicability. *Ped. Transplan*. 1999;3:181-192.

ANDERTON, S.M. Peptide-based immunotherapy of autoimmunity: a path of puzzles, paradoxes, and possibilities. *Immunology*. 2001;104:367-376.

SKYLER, J.S., et al. Effects of oral Insulin in Relatives of patients With Type 1 Diabetes. *Diabetes Care*. 2005;28:1068-1076.

GOODNOW, C.C. Pathways for self tolerance and the treatment of autoimmune diseases. *The Lancet*. 2001;357:2115-2121.

POZZILLI, P., et al. No effect of oral insulin on residual beta-cell function in recent-onset Type I diabetes (the IMDIAB VII). *Diabetol.* 2000;43:1000-1004.

KRAUS, T.A. and MAYER, L. Oral tolerance and inflammatory bowel disease. *Curr. Opin. Gastroenterol.* 2005;21:692-696.

BELL, J.J., et al. In Trans T Cell Tolerance Diminishes Autoantibody Responses and Exacerbates Experimental Allergic Encephalomyelitis. *J. Immunol.* 2008;180:1508-1516.

VON HERRATH, M. and NEPOM, G.T. Animal models of human type 1 diabetes. *Nature Immunol.* 2009;10(2):129-132.

LESLIE, M. Immunology Uncaged. *Science.* 2010;327:1573.

LEGGE, K.L., et al. TCR Agonist and Antagonist Exert In Vivo Cross-Regulation When presented on Igs. J. Immunol. 1998;161:106-111.

VAN DER WORP, H.B., et al. Can Animal Models of Disease Reliably Inform Human Studies? *PLoS Med.* 2010;7(3):1-8.

JAIN, R., et al. Innocuous IFNγ induced by adjuvant-free antigen restores normoglycemia in NOD mice through inhibition of IL-17 production. JEM. 2008;205(1):207-218.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 1-5, 7, 13, 15-19, 22-24, and 26-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method could effectively function as a method for preventing or delaying the onset of type I diabetes (IDDM) in humans.

While the mechanism of action for the method of the instant claims is not disclosed, it appears to require inducing tolerance to a GAD peptide. Tolerance-inducing peptide immunotherapy is well known in the immunological arts. In some cases significant results have been demonstrated in in-bred small animal models. However, said results have not been repeated in human trials. See for example, *Marketletter* (9/13/99) which teaches the complete failure in human trials of two peptides designed for tolerance induction. Both Myloral (for multiple sclerosis, MS) and Colloral (for rheumatoid arthritis, RA) provided successful results in rodent models (EAE and collagen induced arthritis, respectively). See also Leslie (2010) paraphrasing an interview with Dr. Mark Davis wherein Dr. Davis states that in the case of the administration of MBP for tolerance induction to MBP for the treatment of MS, while the method worked in mice, it actually made MS worse in some humans.

More specifically regarding the treatment of diabetes, see Pozzilli et al. (2000) wherein the authors demonstrate that, while the induction of tolerance to orally administered insulin for the treatment of diabetes might have been expected, it simply did not occur. The authors could only speculate as to the reasons for the trial's failure. The authors did note one complicating factor that has been reported several times, and will have to be considered in all future work, a large placebo effect wherein both the treated and control subjects showed similar temporary improvement. Three years later Skyler et al. (2005) reported another failure in one of the largest placebo-controlled tolerance trials ever performed in humans (the administration of insulin for the prevention of type 1 diabetes).

As set forth above, the references demonstrate that peptides that work to induce immune tolerance in *in vivo* small animal disease models cannot be routinely expected to work in humans, i.e., they are unpredictable and requiring of undue experimentation.

Other investigators have discussed additional problems in establishing human tolerance. See, for example, Dong et al. (1999):

> "Despite the fact that it has been relatively easy to induce true tolerance in small experimental animals, translating these studies into larger animals and humans has been much more difficult to achieve. Some of the hurdles that may explain this dilemma are summarized in Table 3. *Even if we have the ideal strategy to use in humans, the lack of reliable predictable assays for rejection or tolerance still does not allow us to know if a patient is truly tolerant so that immunosuppressive agents may be withdrawn*",

emphasis added.

WO 02/053092 teaches that the oral administration of antigens (a route of administration encompassed by the claimed method) for the induction of tolerance presents numerous additional "obstacles", including the problem of accurate dosing given the necessity of digestion which alters both concentration and structure of the antigens. In that work the inventors conclude that:

> "oral and mucosal tolerance cannot be deduced from antigenic activity in conventional immunization, or even *in vitro* results, and must result from extensive empirical experimentation,"

In another attempt to explain these repeated failures Goodnow (2001) states:

> "Obtaining the desired response [tolerance] with these strategies [tolerance induction] is unpredictable because many of these signals [tolerogenic] have both tolerogenic and immunogenic roles,"

(see the Abstract). The author goes on to teach that while the induction of oral tolerance might be considered "an attractive notion", the method has failed in humans because of the lack of understanding of the mechanisms involved (page 2120, column 2).

More recently, Kraus and Mayer (2005) looked at tolerance induction in inflammatory bowel disease (IBD). They reported the ease with which tolerance is induced in in-bred experimental mice and contrasted that with the difficulty in inducing tolerance in humans. Speculating on the reasons for the difference the authors considered a lack of dosing optimization but went on to report that *the mechanisms of tolerance induction in humans and mice appear to be fundamentally different*. Most importantly, Kraus and Mayer report a genetic component wherein many IBD patients and their family members appear to be

incapable of becoming tolerant to oral antigens because they lack the ability to generate the required T regulatory cells. If confirmed, this would mean that *no* tolerance induction regime could work in these patients.

Even more recent work has attempted to duplicate favorable results established in in-bred animal models in a more complex mouse model more realistic to the out-bred human population. See, for example, Bell et al. (2008). The authors employed F_1 hybrid mice (a cross between two in-bred strains) wherein they asked if toleragens that worked in the parent strains would induce tolerance in the crossed F_1 hybrid mice. Unfortunately the results showed that in one instance not only was tolerance not induced, but disease was actually exacerbated. Thus, the work serves as a clear demonstration that the induction of immune tolerance is far from predictable in anything other than carefully chosen in-bred experimental mouse strains.

Also note that Applicant has referred to the NOD mouse as the "gold standard" for diabetes research. Others, however, refer to the NOD mouse as the "workhorse" for diabetes research pointing out the model's limitations. See, for example von Herrath and Nepom (2009). And note that not even all NOD mouse strains are diabetes susceptible, e.g., NOD H-2^k and NOD DQ8 do not develop the disease. Also note that it is well-known that tolerance to GAD is **not** effective for the treatment of diabetes in another well-established diabetes model, the BB rat. Even more recently many scientists have begun to question the value of mouse data altogether. As pointed out by Mark Davis in a recent interview, mice make a "lousy model" for the human immune

system. He refers to mice as a short-lived rodent who's immune system has adapted for scurrying around with its nose in the dirt (Leslie, 2010). Also very recently van der Worp et al. (2010) question the value of using animal data to predict the effectiveness of treatment strategies in human trials. As an example, the authors teach that of about 500 effective treatment strategies for stroke in experimental mice, just 2 have proven effective in humans. The authors cite numerous possible reasons for the failed translation of results, including insufficient statistical power, inadequate animal data, overoptimistic conclusions, flawed studies, and the use of animal models that do not reflect real disease in humans. Finally the reference teaches that neutral and negative animal studies may remain unpublished leading to possibly false impressions of efficacy.

A review of the instant specification shows just a single long example wherein a T cell response to a single insulin B chain peptide (amino acids 9-23) is inhibited in the experimental NOD mouse model of IDDM. First note that the instant claims are drawn to the use of GAD, not insulin, for the suspending, preventing or delaying the onset of IDDM. Thus, the specification offers *no* data in support of the claimed method. Interestingly, the specification discloses, that even regarding the use of an insulin peptide for the suspending, preventing or delaying the onset of IDDM, *the method of the instant claims cannot function as claimed*, (emphasis added). For example, at page 28 of the specification, it is disclosed that, "Soluble Ig-INSβ displayed dose dependent delay of diabetes when given at either stage [pre or post IAA conversion]. However, aggregated Ig-INSβ, which induced IL-10 and TGFβ-producing T cells, thus

involving sustained endogenous IL-10, was protective against diabetes when given before development of insulitis *but had no effect in predisposed mice positive for IAA*", emphasis added. Further, Examples 7 and 9 teach that neither soluble nor aggregated Ig-INSβ can actually prevent IDDM, but rather can only delay onset under specific conditions.

Additionally, Applicant's subsequent work demonstrates that the method of the instant claims would not be expected to function as claimed. See for example Legge et al. (1998). Therein the authors teach that APLs function as, "T cell antagonists, partial agonists, or super agonists" (page 106). The authors go on to teach that PLP-LR stimulated PLP-1 specific T cells (paragraph spanning page 109 and 110), i.e., the T cells that would be pathogenic in an MS patient. Given that *no* experiments have been performed employing GAD peptides and derivatives thereof, it is just as likely that the method of the instant claims would actually exacerbate disease as treat or prevent it.

As set forth in *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297, 1302 (CAFC 2005), enablement cannot be established unless one skilled in the art "would accept without question" an Applicant's statements regarding an invention, particularly in the absence of evidence regarding the effect of a claimed invention. Specifically:

> "As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory

> requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

Thus, in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, the lack of sufficient working examples, i.e., the specification discloses **no** data regarding the treatment or prevention of IDDM employing GAD peptides, and the unpredictability of the art, it would take undue trials and errors to practice the claimed invention.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1-5, 7, 13, 15-19, and 22-24, and 26-30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-7 and 13-16 of U.S. Patent Application No. 11/290,070. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '070 application recite a method comprising treating IDDM with a GAD construct such as would be encompassed by that recited in Claim 1.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

3. Claims 1-5, 7, 13, 15-19, and 22-24, and 26-30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-7 and 13-16 of U.S. Patent Application No. 11/425,084. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '084 application recite a method comprising treating IDDM with a GAD construct such as would be encompassed by that recited in Claim 1.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

4. Claims 1-5, 7, 13, 15-19, and 22-24, and 26-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection for the introduction of new matter into the claims.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) A method comprising the administration of an immunoglobulin construct comprising a protein [fragment] (added 11/12/10) represented by SEQ ID NO:4 (Claims 1 and 13).

Applicant cites pages 13, 21, 45, and 26 in support of the claimed method.

A review of the specification reveals that the peptide of SEQ ID NO:4 is found at page 46 of the specification. The specification, however, does not teach the peptides as part of an immunoglobulin construct.

In the paper filed 5/20/11, Applicant cites pages 4, 8, 19, 22-24, 45, and 46 of the specification in support of the claimed invention.

A review of the cites shows that just the cite at pages 45-46 discloses the peptide of SEQ ID NO:4. The generic

disclosures of "GAD2" at pages 4, 8, 19, and 22-24 cannot support the claimed method employing a specific chimeric construct, said construct comprising the specific amino acid sequence of SEQ ID NO:4 (TYEIAPVFVLLEYVT).

A review of pages 45 and 46, at the beginning of the Examples section, show that the peptide of SEQ ID NO:4 is disclosed just once, and only in the context of a peptide. It is not disclosed in the context of the claimed method of administering an Ig-GAD65 peptide construct for the delaying or preventing of type 1 diabetes. Indeed, the disclosure of the Examples is limited to the production and administration of a single Ig-insulin peptide (Ig-INSβ) and an Ig-hen egg lysozyme (Ig-HEL) control peptide. Even assuming that the cite supports an Ig-GAD65 construct employing the peptide of SEQ ID NO:4, it does not teach said construct comprising a CDR1, CDR2, and CDR3 as is claimed.

5. Claims 1, 2, 4, 5, 7, 13, 15-19, 22-24, 26, and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/30706 in view of Chao et al. (1999).

WO 98/30706 teaches the treatment of autoimmune disorders, including IDDM, (see particularly pages 10 and 19) employing an engineered fusion protein, e.g., a humanized IgG_{2b} chimeric protein wherein an autoantigen peptide is inserted into the D segment of a CDR3 loop (see particularly Figure 1, page 13, and Example II).

The method differs from the claimed invention only in that it does not teach the use of the GAD65 SEQ ID NO:4 peptide as the autoantigen employed for the treatment of IDDM.

Chao et al. teach that the GAD65 peptide of SEQ ID NO:4 (p206-220) is an immunodominant T cell diabetes antigen in their NOD mouse diabetes model (see particularly page 9300, Results).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform the method of WO 98/30706 for the treatment of IDDM in a subject such as a mouse model of diabetes employing the p206-220 T cell autoantigen of Chao et al. One of ordinary skill in the art at the time the invention was made would have had reason to select the GAD65 p206-220 peptide as the autoantigen of choice for use in the claimed method because Chao et al. teaches that it was the most immunodominant diabetes T cell antigen in their model. Regarding the timing of administration of the Ig-fusion protein set forth in claims such as 3, 16, 17, etc., said timing would comprise only routine optimization which would fall well within the purview of one of skill in the art at the time of the invention.

(10) Response to Argument

1. (Appellant's numbering) Appellant begins with statements including, "… no *prima facie* case of lack of enablement has been established", and "… the PTO has not provided any credible evidence showing that one of ordinary skill in the art would ***reasonably doubt*** the asserted utility of the claimed invention

and has therefore not met its initial burden" (emphasis by Appellant).

These sorts of statements raise two issues. First, clearly the record comprises evidence of lack of enablement (no less than a dozen references have been made of record in the rejection and ensuing responses to Appellant's remarks over the course of prosecution), and just as clearly some *prima facie* case for lack of enablement has been made. Whether it is sufficient or not to sustain the rejection is for the Board to decide. Second, it is unclear whether Appellant is arguing against a non-existent rejection for lack of utility, which is mentioned throughout the Brief, or the actual rejection for lack of enablement. There is a difference. Regardless, these and other unreasonable or unsubstantiated allegations in Appellant's opening arguments, as well as at other points throughout the Brief, could cast doubt on the credibility of all of the ensuing arguments.

As Appellant has done throughout the prosecution of this application, Appellant presents a misleading opinion on MPEP 2164.05(a). Note Appellant's not subtle position that the post-filing reference must, "**actually disclose[s] the claimed invention**" (emphasis by Appellant). This is not what the MPEP actually says.

The relevant section of MPEP2164.05(a):

> In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling. Exceptions to this rule could occur if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. *In re Hogan*, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of

> filing and should be considered. In *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993) an article published 5 years after the filing date of the application adequately supported the examiner's position that the physiological activity of certain viruses was sufficiently unpredictable so that a person skilled in the art would not have believed that the success with one virus and one animal could be extrapolated successfully to all viruses with all living organisms. Claims not directed to the specific virus and the specific animal were held nonenabled.

The MPEP says that, "If individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered." Again, there is a difference between Appellant's position and the facts. For example, if a 1999 reference were to state that "no disease caused by a retrovirus has ever been cured" that would be evidence that HIV/AIDS was not curable in 1989. The references provided in this case are analogous.

The examples set forth in MPEP 2164.06(b) are also instructive, in particular examples (B) and (C) in the section **SEVERAL DECISIONS RULING THAT THE DISCLOSURE WAS NONENABLING.** In example (B) a 1988 reference was used to show the non-enablement of a 1983 application. The claims were drawn to a vaccine against the Prague Avian Sarcoma Virus. The reference taught the lack of enablement of a vaccine against the HIV virus. Clearly the reference did not "actually disclose the claimed invention" as Appellant alleges is required for a finding of a lack of enablement. The later showing that a similar treatment was not effective against a related disease was enough to establish a lack of enablement. The teaching of example (C) is also relevant. In this example a 1987 reference was used to establish the lack of enablement of the claims of a 1985 application. In this instance the Examiner showed that the

claimed method would not function in a more complex biological system. This is analogous to the situation here wherein immune tolerance is easily established in some strains of inbred laboratory mice, yet the documentation of record shows that tolerance induction has repeatedly failed to be inducible in the more complex outbred human population.

Further regarding immune tolerance, Appellant has stated that the claims are not drawn to a method of establishing immune tolerance. This issue has been addressed throughout the prosecution of this application. As set forth in the specification at page 3, the specification discloses that the Invention comprises, among other things, the use of an Ig construct wherein an autoantigen is inserted into a CDR3 region and administered for the induction of immune tolerance for the treatment of an autoimmune disease. The specification cites the Inventors' own work using the same Ig construct with a different autoantigen (proteolipid protein, PLP) for the treating of a different autoimmune disease (experimental allergic encephalomyelitis, EAE) through the, "induction of tolerance rather than immunity" (page 3). See also page 29, wherein a “tolerance-like mechanism against diabetogenic T cells” is disclosed.

Appellant discounts the teachings of several of the cited references and ignores the rest.

Regarding those references discounted, the *Marketletter* publication and Pozzilli et al. are discounted because they do not anticipate the claimed invention. The references do,

however, show that in three specific instances, comprising the attempted treatment of three different autoimmune diseases, including diabetes, laboratory immune tolerance induction in inbred laboratory mice failed to be achievable in the more complex outbred human population. Likewise Dong et al. and Goodnow are discounted because they do not anticipate the claimed invention. The references do, however, provide acknowledgement that laboratory results achieving immune tolerance induction in inbred laboratory mice failed to be achievable in the more complex outbred human population, for reasons unknown, but speculated to possibly be that humans are simply more complex and the mechanisms of immune tolerance are not well understood. Interestingly, Appellant simply dismisses without reason the Inventor's own work in Legge et al.

Appellant argues that the specification teaches how to make and use the claimed invention.

The specification does not teach how to prevent or delay the onset of type 1 diabetes in a human subject employing the GAD2-Ig construct of the instant claims. In particular, as set forth in the rejection, the method at best delays the onset of disease in some experimental mice using an unrelated construct. This showing is clearly insufficient support for claims that encompass the use of a different construct and further encompass the prevention of disease.

Appellant cites a 1.132 declaration previously submitted by the Inventor showing that the IgGAD2 construct of the instant claims could delay hyperglycemia in the NOD experimental mouse

model. Appellant further refers to the NOD mouse model as the "gold standard animal model".

Appellant's position seems to be that while post-filing demonstrations of a lack of enablement are impermissible, post-filing demonstrations of enablement are permissible. Said position would seem to be contradictory. Turning again to *In re Wright*, the court dismissed the post-filing submissions of the Inventor, stating, "all of these developments occurred after the effective filing date of Wright's application and are of no significance regarding what one skilled in the art believed as of that date." Regarding the NOD mouse model comprising the "gold standard animal model", distinguished immunologists such as Gerald Nepom and Matthias von Herrath have referred to the NOD model as a "workhorse" with numerous limitations, see von Herrath and Nepom (2009, of record). They note that just one of several NOD mouse strains even develops diabetes. They further note the ease of treating diabetes in the single NOD strain susceptible to diabetes, i.e., "over 200 perturbations of the immune environment are known that can prevent or reverse disease in NOD mice," treatments that have proven to be ineffective in humans (see Box 1). They conclude that the single strain of NOD mouse is susceptible to diabetes because of, "a rather unique set of genotypic circumstances that is unlikely to exist in a substantial fraction of the human population, if it exists at all" (page 130, column 1).

Citing *In re Brana* Appellant argues that the treatment of humans is not required

Appellant's reliance on the findings in *Brana* is clearly misplaced. The fact pattern in *In re Brana* little resembles the fact pattern in this case. First, the claimed invention in *Brana* was a product, not a method of treatment. Thus, the enablement requirement was far different. There was no requirement that the invention be enabled for its full scope as with a method. Second, there was a showing that closely related compositions did have anti-cancer activity. But most importantly, there was no showing that *similar and closely related methods did not work in humans* as there is in this case. Experimental data derived from animal models is indeed accepted when no human data is available. But in this instance human data is available and cannot simply be ignored. And as set forth above, while the NOD mouse model may be art-recognized it is also art-recognized as disappointingly limited.

2. and 3. Appellant argues that the obviousness type double patenting rejections are provisional and should be withdrawn upon allowance.

As the oldest of the cases under obviousness type double patenting rejection upon the finding of otherwise allowable subject the instant rejections obviousness type double patenting will be withdrawn.

4. Appellant cites eight bullet points in support of the claimed method.

None of the bullet points cited by Appellant disclose the generic immunoglobulin-GAD2 construct employed in the method of

the instant claims. As most broadly claimed, the method employs the GAD2 peptide of SEQ ID NO:4 inserted *anywhere* into *any* immunoglobulin comprising a variable region, said variable region comprising *any* CDR1, CDR2, and CDR3. "Ig-GAD2" comprises just a single species of the generic construct of the claimed method, and a careful review of the specification reveals that even "Ig-GAD2" is not fully described because the specification does not disclose precisely where in the immunoglobulin the GAD2 peptide of SEQ ID NO:4 is inserted. Further, while likely, nowhere in the specification is it actually disclosed that "Ig-GAD2" is the construct of the narrowest claim, Claim 24.

5. Appellant argues that an obviousness rejection that relies on an alleged teaching, suggestion, or motivation *must* be articulated in a *Graham v. Deere* format.

Appellant is simply in error, the *Graham v. Deere* format is just one of many that may be used in a finding of obviousness. And even if a rejection based on a teaching, suggestion, or motivation is made, it is no longer required that the *Graham v. Deere* format be followed precisely. It is the substance of a rejection, not the format that is critical.

Appellant argues a lack of expectation of success.

Appellant's argument seems puzzling given the fact that as of the effective filing date of the instant application the record contains *no* evidence that Appellant had ever successfully performed the method of the instant claims, even in their limited inbred small animal model. If persuasive, Appellant's

argument would *require* a rejection for lack of enablement. And it is unclear how Appellant can convincingly ignore the Inventor's own teaching (in WO 98/30706) that the Ig chimeric construct employed in the method of the instant claims can be employed in the treatment of various T cell mediated disorders, including insulin dependent (type 1) diabetes, by simply changing the antigen (pages 10 and 19). Appellant cannot now credibly argue that the Inventor's own teachings should be ignored because it is convenient.

Appellant argues a lack of rationale in the record for the selection of the peptide of SEQ ID NO:4 for use in the construct of the claimed method.

As set forth in the rejection the peptide of SEQ ID NO:4 was identified by Chao et al. as immunodominant. It would have been obvious to the ordinarily skilled artisan at the time of the invention to choose an immunodominant epitope in a method of inducing immune tolerance to said epitope.

Citing post-filing art Jain et al. (2008), Appellant argues unexpected results.

A persuasive claim of unexpected results requires that the unexpected results be commensurate in scope with the invention as claimed. Such is not the case here. The claimed method employs a generic Ig-GAD2 construct wherein the GAD2 peptide of SEQ ID NO:4 is inserted *anywhere* into *any* immunoglobulin comprising a variable region, said variable region comprising *any* CDR1, CDR2, and CDR3. Employing just a single construct,

Jain et al. clearly does not teach anything even approaching the scope of the claimed method. Further note that the cited reference teaches nothing regarding the claimed method of delaying or preventing type 1 diabetes. Additionally, evidence of unexpected results generally takes the form of a direct comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. In this instance it is noted that no comparison with any other treatment has been performed; Appellant merely speculates that, "the presently claimed soluble Ig-GAD2 composition provides unexpected results in that it has the ability to rescue residual and form new insulin-producing β cells." Accordingly, Appellant's allegation of unexpected results is not persuasive.

Appellant argues that the claims require autoantibody seroconversion prior to the administration of the claimed construct.

It is well-settled that the routine optimization of a claimed method is obvious. In this instance autoantibody seroconversion is a routine first observation in the development of type 1 diabetes, and an obvious time point at which to begin treatment. Clearly, it would not generally be obvious to administer a treatment before the first sign of disease, nor would it be possible to delay or prevent disease after its onset.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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